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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/269,321	09/13/1999	WILLIAM KAELIN JR.	46793	9798

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EXAMINER	
SANDALS, WILLIAM O	
ART UNIT	**PAPER NUMBER**
1636	24

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/269,321	KAELIN JR. ET AL.	
	Examiner	Art Unit	
	William Sandals	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 September 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Claims 15-27 are pending.

Claims 15-23 and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al.

Claims 15-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al. as applied to claims 15-23 and 25-27 above, and further in view of US 6,310,045 (Barber et al.).

The Declaration of William Kaelin under 37 CFR 1.132 filed May 30, 2003 is insufficient to overcome the rejection of claims 15-27 based upon 35 USC 103(a) as set forth in the Office action mailed November 19, 2002. The response to the declaration is set forth following the repeated rejection below.

Drawings

New corrected drawings are required in this application because corrections to drawings as indicated in the Draftsmans review mailed on March 23 2000, in Paper No. 9 must be submitted, and are no longer permitted to be held in abeyance as set forth in the MPEP 608.02(b). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-23 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al.

The claims are drawn to a method of selectively expressing a gene in a malignant cell comprising determining if the malignant cell expresses a sufficient amount of E2F to cause expression of a gene of interest operably linked to an E2F responsive promoter, then adding an effective amount of a nucleic acid cassette comprising an E2F responsive promoter operably linked to a gene of interest to the malignant cell. The gene of interest encodes a protein that stimulates production or expression of a cellular product, a positive potentiator or encodes a gene that inhibits production or expression of a cellular product, a negative potentiator. The cell is transduced with the nucleic acid cassette. Selectively expressing the gene by inducing the E2F responsive promoter with the E2F, which has been determined to be present in the cell. The E2F responsive promoter may be from a group of known E2F responsive promoters. The gene of interest may be a cytokine, a dominant negative mutant, and a cytotoxin, which may be a suicide gene, which may be HSV TK. The nucleic acid

cassette may be present in a viral vector. The malignant cell may be from a solid tumor, which may be a glioma.

McCormick teaches a method of selectively expressing a gene of interest in a neoplastic (malignant) cell with a nucleic acid cassette comprised in a viral vector (see page 4, line 23 – page 5, line 6). McCormick teaches that the gene of interest may be operably linked to an E2 promoter (see page 7, lines 1-20 and page 27, lines 1-23). McCormick teaches the use of HSV TK gene. McCormick teaches the transduction of the neoplastic cell with the viral vector, and expressing the gene of interest in the neoplastic cell.

McCormick does not teach that the expression of E2F is determined in the neoplastic cell. McCormick does not teach the various E2F responsive promoters, nor that the malignant cell may be a glioma.

Raj et al. teach that gliomas produce E2F. Raj et al. teach the various E2F responsive promoters (see page 1279, col. 2). Raj. et al. teach that E2F levels may be determined in malignant cells (see figure 3). Raj. et al. teach the introduction of a nucleic acid cassette comprising an E2F responsive promoter operably linked to a gene of interest, into a malignant cell (see page 1285).

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to combine the method of selectively expressing a gene of interest operably linked to an E2F responsive promoter in a malignant cell as taught by McCormick with the E2F responsive gene of Raj et al. because McCormick and Raj et al. were expressing genes of interest which were operably linked to E2 responsive

promoters. One of ordinary skill in the art would have been motivated to combine the above teachings of McCormick and Raj et al. for the expected benefit of expressing a gene of interest in a malignant cell, where the malignant cell is expressing sufficient E2F to induce expression from the E2F responsive promoters. Further, one of ordinary skill in the art would have had a reasonable expectation of success given the teachings of McCormick who demonstrate the expression of a gene of interest operably linked to an E2F responsive promoter and Raj et al. who demonstrate the expression of a gene of interest operably linked to an E2F responsive promoter.

Claims 15-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18992 (McCormick) in view of Raj et al. as applied to claims 15-23 and 25-27 above, and further in view of US 6,310,045 (Barber et al.).

The claims are drawn to the invention described above, and where the cytotoxin is domain III of Pseudomonas exotoxin A.

McCormick and Raj et al. teach the invention as described above.

McCormick and Raj et al. do not teach that the cytotoxin is domain III of pseudomonas exotoxin A.

Barber et al. teach cytotoxins such as HSV TK and domain III of pseudomonas exotoxin A encoded in genes of interest (see the summary, cols. 2-3). The cytotoxins are well known to be comprised in viral vectors and used in methods of expression to kill malignant cells (see cols, 5-7). Barber et al. teach that HSV TK and domain III of

pseudomonas exotoxin A are equivalents for the use as a cytotoxin expressed in a viral vector for killing malignant cells (see cols. 6-7).

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to combine the method of selectively expressing a gene of interest operably linked to an E2F responsive promoter in a malignant cell as taught by McCormick with the E2F responsive promoters of Raj et al. and the cytotoxic genes of Barber et al. because McCormick was expressing genes of interest operably linked to E2 responsive promoters where the cytotoxic gene may be a cytotoxin such as HSV TK, Raj et al. taught E2F responsive promoters operably linked to a gene of interest expressed in a malignant cell, and Barber et al. taught the equivalence of the HSV TK cytotoxic gene and the gene encoding the domain III of pseudomonas exotoxin A which are expressed in malignant cells and are useful for killing the malignant cells. One of ordinary skill in the art would have been motivated to combine the above teachings of McCormick , Raj et al. and Barber et al. for the expected benefit of expressing a cytotoxic gene of interest in a malignant cell, where the malignant cell is expressing sufficient E2F to induce expression from the E2F responsive promoters operably linked to cytotoxic genes. Further, one of ordinary skill in the art would have had a reasonable expectation of success given the teachings of McCormick who demonstrate the expression of a gene of interest operably linked to an E2F responsive promoter, Raj et al. who demonstrate the expression of a gene of interest operably linked to an E2F responsive promoter and Barber et al. who teach the equivalence of the HSV TK cytotoxic gene and the gene encoding the domain III of pseudomonas exotoxin A.

Response to Arguments

Arguments are set forth at pages 2-3 in Paper No. 22, filed May 19, 2003 asserting that the declaration of Dr. Kaelin states that neither McCormick nor Raj et al. teach or suggest the instant claimed invention. The argument is framed around the declaration of Dr. Kaelin. Dr. Kaelin states that the references are directed to "the role of E2F as a simple on/off trigger for gene expression", and that Raj et al. teach that "association of E2F1 with these various cellular proteins appears to be cell cycle regulated, with the appearance of distinct complexes at precise states of the cell cycle". The declaration goes on to assert that Raj et al. teach that E2F is either "on" (when not bound to pRB) or "off" (when bound to pRB). It is further asserted that the E2F binding sites on E2F responsive promoters bind to a complex called "Glial E2F1 – associated proteins (GEAPs)" The proteins of the GEAP complexes have a distinct molecular mass. E2F protein is not found in the GEAP complexes.

It is asserted in Paper No. 22, page 3 (also in the declaration of Dr. Kaelin at paragraphs 8-10) that Raj et al. provides no basis for looking at levels of free E2F.

It is asserted in paper No. 22 at page 3 (also in the declaration of Dr. Kaelin at paragraph 13) that that "prior to our work, the expectation would be that E2F-responsive promoters would be activated in rapidly proliferating normal cells as well as in tumor cells".

Independent instant claim 25 is drawn to a method of selectively expressing a gene in a malignant cell comprising determining if the malignant cell expresses sufficient E2F to cause expression of a gene operably linked to an E2F responsive

promoter. There is no limitation directed to "free E2F", nor is there a limitation to E2F promoters being "activated". Further, there is no limitation to distinguish between expression in a malignant cell versus expression in a normal proliferating cell. Thus, the arguments based on these limitations is not found persuasive.

Raj et al. discuss the presence of E2F in the glioma cells. The E2F is used in binding assays with E2F responsive promoters (see for example, figure 2). This is an assay of E2F in the cells. Raj et al. discuss the presence of E2F in glioma cells, and assay for E2F activity in glioma cells (see figure 3). Therefore, Raj et al. teach the determination of the presence of E2F in glioma cells sufficient for activation of an E2F responsive promoter. Raj et al. discuss at page 1285, column 2 the importance of E2F in U-87MG cells (human glioma cells) for activation of the endogenous E2F responsive promoters. Raj et al. teach the transfection of U-87MG cells with an E2F1 gene to test the responsiveness of the U-87MG cells to the overexpression of E2F1. The E2f1 gene is operably linked to an E2F responsive promoter. The endogenous E2f in the cell causes expression of the recombinant E2F protein. Therefore, the arguments that Raj et al. is directed to an "on/off" condition for E2F expression is not found convincing. Further, regarding the assertion that the teachings of Raj et al. are directed to GEAPs, is not found convincing because of the above stated reasons.

Arguments presented in Paper No. 22, page 4, assert that the declaration of Dr. Kaelin states at paragraphs 14-15, that an E2F responsive promoter linked to a suicide reporter gene in normal cells revealed that E2F present in the normal cells did not induce the suicide reporter gene and thus did not kill the normal cells, but that the same

construct expressed in malignant cells did kill the cells. Thus, these experiments suggest a positive feedback loop in tumor cells. It is asserted that Raj et al. does not suggest or teach that one of ordinary skill in the art would look at E2F expression levels.

Raj et al. teach at the introduction that it is known that malignant cells express E2F at high levels. Therefore, Raj et al. teach that one of ordinary skill in the art does look at E2F expression levels in normal and malignant cells. The arguments regarding the overexpression of E2F in malignant cells which results in the killing of the transfected cells and arguments regarding the existence of a positive feedback loop are not commensurate with the limitations of the claims, and therefore, are not found persuasive.

Arguments presented in Paper No. 22 at page 5 assert that the declaration of Dr. Kaelin at paragraph 19, concludes that tumor selectivity and the importance of looking for E2F expression in malignant cells is in no way suggested by the prior art references.

These arguments are directed to limitations which are not present in the claims and are not commensurate with the limitations of the claims, and therefore, are not found persuasive.

Arguments presented in Paper No. 22 at page 5 assert that one of ordinary skill in the art would not know that one could selectively express cytotoxic genes in a malignant, but not a normal cell. It is asserted that the ordinary skilled artisan would be concerned that there would be substantial harm to normal cells resulting from the use of cytotoxins.

Claim 25 is drawn to selectively expressing a gene in a malignant cell. The rejection above makes the selective expression of a gene operatively linked to an E2F promoter obvious to one of ordinary skill in the art. McCormick teaches the desirable and beneficial use of a cytotoxic gene operatively linked to an E2 promoter in a malignant cell. This teaching is clear and direct. Therefore, the argument is not found convincing.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William Sandals whose telephone number is (703) 305-1982. The examiner can normally be reached on 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers

for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

William Sandals
August 11, 2003

JAMES KETTER
PRIMARY EXAMINER